DATA EVALUATION RECORD

AE 1170437 (DIAMINOTRIAZINE)

Study Type: OPPTS 870.3150 [§82-1b]; Subchronic Oral Toxicity Study in Dogs

Work Assignment No. 5-01-203 C (MRID 47443289)

Prepared for
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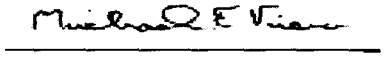
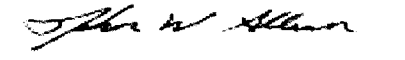
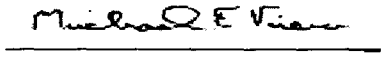
Primary Reviewer: Michael E. Viana, Ph.D., D.A.B.T.	Signature:  Date: 1/30/09
Secondary Reviewer John W. Allran, M.S.	Signature:  Date: 1/30/09
Program Manager: Michael E. Viana, Ph.D., D.A.B.T.	Signature:  Date: 1/30/09
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DATA EVALUATION RECORD

STUDY TYPE: Subchronic Oral Toxicity in Dogs (gavage); OPPTS 870.3150 ['82-1b]; OECD 409.

PC CODE: 129108 **DP BARCODE:** D356856
TXR #: 0054980

TEST MATERIAL (PURITY): AE 1170437 (Diaminotriazine; 94.5-99.4% a.i.)

SYNONYMS: BCS-AA10717; *N*-[(1*R*,2*S*)-2,3-dihydro-2,6-dimethyl-1*H*-inden-1-yl]-6-(1-fluoroethyl)-1,3,5-triazine-2,4-diamine; Indaziflam

CITATION: Eigenberg, D.A. (2008) A 90-day toxicity study in the beagle dog with technical grade BCS-AA10717 administered by oral gavage. Bayer CropScience LP, Toxicology, Stilwell, KS. Laboratory Study No.: 06-S16-DL Report No. 201630, June 26, 2008. MRID 47443289. Unpublished.

SPONSOR: Bayer AG, Bayer CropScience, Alfred Nobel Str. 50, 40789 Monheim, Germany

EXECUTIVE SUMMARY: In a subchronic oral toxicity study in dogs (MRID 47443289), BCS-AA10717 (AE 1170437, Diaminotriazine; 94.5-99.4% a.i.; Batch Nos. NLL 7482-5A and EFIM000511) in 0.5% aqueous methyl cellulose was administered via daily oral gavage in a dose volume of 1 or 5 mL/kg to four beagle dogs/sex/dose group at doses of 0, 7.5 15, or 30 mg/kg/day for at least 90 days. On Day 23, dosing was halted in the 30 mg/kg/day group, and resumed on Day 25 at 15 mg/kg given twice daily approximately 7-8 hours apart.

No adverse, treatment-related effects were observed on food consumption, ophthalmoscopic examinations, hematology, clinical chemistry, urinalysis, organ weights, or gross pathology.

At 15 mg/kg/day, treatment-related findings were observed in the nervous system. In the males, slight multifocal axonal degeneration of the sciatic nerve was observed in 1/4 dogs, and minimal multifocal axonal degeneration of the spinal cord was noted in 1/4 dogs, both compared to 0 controls. In the females, minimal multifocal axonal degeneration was observed in the brain in 1/4 dogs, minimal focal/multifocal axonal degeneration was observed in the sciatic nerve in 2/4 dogs, and minimal to moderate multifocal axonal degeneration of the spinal cord was noted in 2/4 dogs, all compared to 0 controls.

At 30 mg/kg/day, three dogs presented with seizures on Days 15, 22, and 35, respectively, and were killed on the day the seizures were observed. Treatment-related clinical findings observed in these dogs included the following: seizures in the male; aggressive, tremors, ataxia (unsteady), labored breathing, pupil no reaction to light or sluggish, decreased activity, circling, seizures, and sores due to seizures in the females. Due to the seizures, dosing of the 30 mg/kg/day group was halted on Day 35, and the surviving dogs of this group were euthanized on Day 36 for humane reasons. Additionally at this dose, male dogs displayed decreased body weight gains for Days 0-35 compared to all other groups, while females lost weight during this period compared to the other groups. Treatment-related findings were observed in the nervous system. In the males, slight multifocal axonal degeneration of the sciatic nerve was observed in 1/4 dogs, and minimal to moderate multifocal axonal degeneration of the spinal cord was noted in 4/4 dogs, both compared to 0 controls. In the females, minimal to slight multifocal axonal degeneration was observed in the brain in 2/4 dogs, minimal to slight focal/multifocal axonal degeneration was observed in the sciatic nerve in 2/4 dogs, and minimal to moderate multifocal axonal degeneration of the spinal cord was noted in 4/4 dogs, all compared to 0 controls.

The LOAEL is 15 mg/kg/day, based on axonal degeneration in the nervous system of both sexes. The NOAEL is 7.5 mg/kg/day.

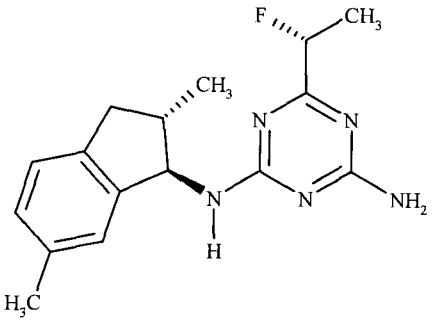
This study is classified **acceptable/guideline** and satisfies the guideline requirements (OPPTS 870.3150; OECD 409) for a subchronic oral toxicity study in dogs.

COMPLIANCE: Signed and dated Data Confidentiality, GLP Compliance, Flagging, and Quality Assurance statements were provided.

I. MATERIALS AND METHODS

A. MATERIALS

1. Test material(s): BCS-AA10717 technical (AE 1170437; Diaminotriazine)

Description:	White or light beige powder
Batch Nos.:	NLL 7482-5A[1] (on Study Day 0) and EFIM000511[2] (remainder of study)
Purity:	99.4%[1] and 94.5%[2] a.i., respectively
Stability:	Stable in the vehicle for up to 7 days at room temperature
CAS #:	950782-86-2 (changed from 730979-19-8)
Structure:	

2. Vehicle: 0.5% aqueous methyl cellulose

3. Test animals

Species:	Dog
Strain:	Beagle
Age and weight at initiation of treatment:	6-7 months; 6.6-8.6 kg males, 5.4-7.2 kg females
Source:	Marshall BioResources (North Rose, NY)
Housing:	Individually in stainless steel runs
Diet:	Harlan Teklad® Global 25% Protein Certified Dog Diet #2025C (Harlan Laboratories, Madison, WI), *ad libitum*, except when dogs were fasted overnight prior to blood collection
Water:	Tap water, *ad libitum*
Environmental conditions	
Temperature:	18-29°C
Humidity:	30-70%
Air changes:	At least 14/hour
Photoperiod:	12 h light/12 h dark
Acclimation period:	Seven days

B. STUDY DESIGN

1. In life dates: Start: 02/16/06 End: 05/19/06

2. Animal assignment: The dogs were randomly assigned (stratified by body weight) to the following groups shown in Table 1.

TABLE 1: Study design [a]						
Test group	**Dose group (mg/kg/day)**	**# of dogs/sex**	**Dose volume Days 0-22 (mL/kg)**	**Concentration (mg/mL)**	**Dose volume Days 23-end (mL/kg)**	**Concentration (mg/mL)**
Control	0	4	1	0	5	0
Low dose	7.5	4	1	7.5	5	1.5
Mid dose	15	4	1	15	5	3.0
High dose[b]	30	4	1	30	5	3.0

a Data were obtained from page 15 of the study report.
b Dosing was halted on Day 23 and resumed on Day 25 as 15 mg/kg administered twice/day approximately 7-8 h apart.

3. **Dose-selection rationale:** It was stated that the doses used for this study were based on a 90-day dose range-finding study (Study No. 05-P16-ZY, Bayer CropScience Report No. 201545; not provided). In this study, compound-induced seizures occurred in both sexes at a dose level of 50 mg/kg/day. No further information was provided.

4. **Dose preparation, administration, and analysis:** Dose formulations were prepared once a week and stored refrigerated. Although not stated, the reviewers assume that for each dose level, a weighed amount of the test material was suspended in an appropriate volume of 0.5% aqueous methyl cellulose to achieve the desired concentration. It was stated that the dosing mixtures were prepared without adjusting for purity. Dose formulations were administered via oral gavage daily. Animals received a dose volume of 1 mL/kg body weight on Days 0-22, changing to 5 mL/kg body weight for Days 23-end (Table 1). The administered volumes were adjusted weekly based upon the individual body weights. The dose formulations were constantly stirred prior to drawing the dose into the dosing syringe. After dosing, the gavage tube was flushed with 3 mL of the vehicle. Analyses for determination of homogeneity and stability of the test substance in the vehicle were conducted on formulations with concentrations of 1, 3, and 40 mg/mL; concentration analyses were performed on all dose levels on Weeks 1, 2, 3, 7, 12, and 13. Homogeneity was measured on five samples (sampling locations not specified) of the dose suspensions. Stability was measured in three samples (sampling location not specified) after 1 and 7 days at room temperature.

Results

Homogeneity (% RSD): 1.0-1.9%

Stability (% initial): 102-107% on Day 7

Concentration (mean % nominal) 89-103%

The 1.5 mg/mL formulation was found to be below criteria on Weeks 12 and 13 (79% of nominal), causing the mean concentration of this concentration (89% of nominal) to be slightly below the in-house standard of 100±10%. The analytical data indicated that the mixing procedure was adequate and that the variation between nominal and actual dosage to the animals was acceptable.

5. **Statistics:** Significance was reported at $p \leq 0.05$ for all tests except Bartlett's test ($p \leq 0.001$). All tests were two-tailed, except for evaluations of gross and microscopic pathological lesions which were one-tailed. Continuous data were analyzed with Bartlett's test for homogeneity of the variances. If the variances were homogeneous, an ANOVA was performed, followed by Student's t-test on parameters showing a significant effect by ANOVA. If the variances were not homogeneous, a Kruskal-Wallis ANOVA was performed, followed by the Mann-Whitney-U test to identify statistical significance between groups. Frequency data were initially analyzed by a Chi-square procedure, followed by a Fisher's Exact Test if statistical significance was found.

   Although it would be more customary to use Dunnett's test to compare treated groups with controls for parametric data, the statistical analyses were considered appropriate.

C. METHODS

1. **Observations:** Cage-side examinations for mortality and clinical signs of toxicity were performed twice daily (once daily on weekends and holidays). Detailed clinical observations were performed at study initiation and weekly thereafter.

2. **Body weight:** The weight of each dog was recorded prior to initiation of treatment, weekly during dosing, and immediately prior to necropsy.

3. **Food consumption:** Each dog's food consumption was recorded daily, and mean consumption (g/dog/day) was presented for each day.

4. **Ophthalmoscopic examination:** The eyes of all dogs were examined for pupillary reflex; the pupils were then dilated for external and internal examinations. Examinations were conducted on all dogs prior to study initiation and in all surviving animals just prior to study termination.

5. **Hematology and clinical chemistry:** Blood samples were collected from the jugular vein of overnight fasted dogs prior to initiation of treatment and during Weeks 5, 9, and 13. The following CHECKED (X) parameters were examined.

a Hematology

X	Hematocrit (HCT)*	X	Leukocyte differential count*
X	Hemoglobin (HGB)*	X	Mean corpuscular HGB (MCH)*
X	Leukocyte count (WBC)*	X	Mean corpuscular HGB concentration (MCHC)*
X	Erythrocyte count (RBC)*	X	Mean corpuscular volume (MCV)*
X	Platelet count*	X	Reticulocyte count
	Blood clotting measurements*	X	Blood cell morphology
X	(Activated partial thromboplastin time)	X	Red blood cell distribution width (RDW)
	(Clotting time)	X	Hemoglobin distribution width (HDW)
X	(Prothrombin time)		

* Recommended for 90-day oral non-rodent studies based on Guideline 870.3150

b. Clinical chemistry

	ELECTROLYTES		OTHER
X	Calcium*	X	Albumin*
X	Chloride*	X	Creatinine*
	Magnesium	X	Urea nitrogen*
X	Phosphorus*	X	Total cholesterol*
X	Potassium*	X	Globulins
X	Sodium*	X	Glucose*
	ENZYMES (more than 2 hepatic enzymes eg.,*)	X	Total bilirubin*
X	Alkaline phosphatase (ALP)*	X	Total protein (TP)*
	Cholinesterase (ChE)	X	Triglycerides
X	Creatine phosphokinase		Serum protein electrophoresis
X	Lactic acid dehydrogenase (LDH)	X	Albumin/globulin ratio
X	Alanine aminotransferase (also SGPT)*	X	Uric acid
X	Aspartate aminotransferase (also SGOT)*		
	Sorbitol dehydrogenase*		
X	Gamma glutamyl transferase (GGT)*		
	Glutamate dehydrogenase		

* Recommended for 90-day oral non-rodent studies based on Guideline 870.3150

6. **Urinalysis:** Urinalysis was performed prior to initiation of treatment and during Weeks 5, 9, and 13. The method of collection was not provided; however, the study protocol specified a 24-h collection period. The CHECKED (X) parameters were examined.

X	Appearance*	X	Glucose*
X	Volume*	X	Ketones
X	Specific gravity / osmolality*	X	Bilirubin
X	pH*	X	Blood / blood cells*
X	Sediment (microscopic)	X	Nitrite
X	Protein*	X	Urobilinogen
		X	Leukocytes

* Recommended for 90-day oral non-rodent studies based on Guideline 870.3150

7. **Sacrifice and pathology:** All animals were euthanized by an intravenous injection of Fatal-Plus® (Vortech Pharmaceuticals, Dearborn, MI). All animals were subjected to a gross necropsy. The CHECKED (X) tissues were collected for microscopic examination. The (XX) organs, in addition, were weighed from all animals.

	DIGESTIVE SYSTEM		CARDIOVASC./HEMAT.		NEUROLOGIC
	Tongue	X	Aorta, thoracic*	XX	Brain* +
X	Salivary glands*	XX	Heart* +	X	Peripheral nerve (sciatic)*
X	Esophagus*	X	Bone marrow*	X	Spinal cord (3 levels)*
X	Stomach*	X	Lymph nodes*	XX	Pituitary*
X	Duodenum*	XX	Spleen* +	X	Eyes (optic nerve)*
X	Jejunum*	XX	Thymus* +		GLANDULAR
X	Ileum*			XX	Adrenal gland* +
X	Cecum*		UROGENITAL		Lacrimal gland
X	Colon*	XX	Kidneys* +	XX	Parathyroid* + [b]
X	Rectum*	X	Urinary bladder*	XX	Thyroid* + [b]
XX	Liver* + [a]	XX	Testes* +		OTHER
XX	Gall bladder* + [a]	XX	Epididymides* +	X	Bone (rib, sternum)
X	Pancreas*	XX	Prostate*	X	Skeletal muscle
	RESPIRATORY	XX	Ovaries (with oviducts)* +	X	Skin*
X	Trachea*	XX	Uterus* +	X	All gross lesions and masses*
XX	Lungs*	X	Mammary gland (females)*		
X	Nasal cavity*	X	Vagina		
X	Pharynx*	X	Cervix		
X	Larynx*	X	Ureter		

a The liver and gall bladder were weighed together
b The parathyroids were weighed with the thyroid.
* Recommended for 90-day oral non-rodent studies based on Guideline 870.3150
+ Organ weight required for non-rodent studies.

All tissues were preserved in 10% buffered formalin, except the eyes and optic nerves (Davison's fixative), and testes and ovaries (Bouin's fixative). Tissue samples were processed routinely and stained with hematoxylin and eosin; additionally, selected sections of brain, spinal cord, and peripheral nerve were stained with Luxol Fast Blue/Cresyl Violet and Sevier Munger silver stain. All gross lesions; prostate and liver from all males; brain, spinal cord, and peripheral nerve from all animals; and remaining tissues (except the vagina) in the control, 15, and 30 mg/kg/day groups were examined microscopically. Microscopic pathological findings were graded as normal, minimal, mild or slight, moderate, marked, or severe. Mean severity scores were calculated and presented.

II. RESULTS

A. OBSERVATIONS

1. **Mortality:** No dogs were found dead. Three 30 mg/kg/day dogs (male DL3004, female DL3102, and female DL3103) presented with seizures on Days 15, 22, and 35, respectively, and were killed on the day the seizures were observed. Due to the seizures, dosing of the 30 mg/kg/day group was halted on Day 35, and the surviving dogs of this group were euthanized on Day 36 for humane reasons.

2. **Clinical signs of toxicity:** Treatment-related clinical findings were observed in the three 30 mg/kg/day dogs that were killed. The male (DL3004) was observed with seizures. One

female (DL3102) was noted with the following findings: aggressive, whole-body tremors, ataxia (unsteady), labored breathing, left pupil no reaction to light, right pupil sluggish, seizures, and sores due to the seizures. The other female (DL3103) was observed with the following: aggressive, whole-body tremors, ataxia (unsteady), decreased activity, circling, pupils sluggish, and seizures.

Increased salivation was noted at 15 mg/kg/day in 3/4 females and at 30 mg/kg/day in 3/4 males and 3/4 females; however, this finding was generally observed pre-dosing or at dosing and was considered to be a Pavlovian-like response. One 15 mg/kg/day female was observed with tremors on Day 48; however, this single observation was not considered adverse. All other clinical findings occurred at similar frequency in all groups or were unrelated to dose.

B. BODY WEIGHT AND WEIGHT GAIN: Body weight and body weight gain data are presented in Table 2. At 30 mg/kg/day, male dogs displayed decreased body weight gains for Days 0-35 compared to all other groups (57.7 g compared to 508.2-719.0 g), while females lost weight (-76.3 g) during this period compared to the other groups (51.3-489.3 g). There were no effects of treatment observed on body weights or body weight gains in the 7.5 or 15 mg/kg/day groups.

TABLE 2. Selected mean (±SD) body weights and body weight gains (g) in dogs administered BCS-AA10717 by oral gavage for up to 90 days[a]

Study Day	Dose (mg/kg/day)			
	0	7.5	15	30
Males				
0	7201.3±623.9	7763.3±704.3	7648.0±779.7	7656.3±582.6
7	7571.8±696.5	8033.8±660.2	7821.3±662.8	7670.3±592.9
35	7920.3±721.5	8271.5±606.5	8195.8±1085.6	7714.0±505.0
BWG Days 0-35[b]	719.0	508.2	547.8	57.7
84	8332.5±871.6	8945.3±1203.4	8883.5±980.6	---
BWG Days 0-84[b]	1131.2	1182.0	1235.5	
Females				
0	6768.0±368.6	6570.3±377.2	6212.0±712.4	6426.3±327.2
7	6804.3±453.0	6687.5±420.4	6439.8±525.4	6632.5±546.6
35	6819.3±766.1	6704.5±593.7	6701.3±437.5	6350.0±363.6
BWG Days 0-35[b]	51.3	134.2	489.3	-76.3
84	7232.8±546.3	7426.5±727.9	7048.5±508.2	---
BWG Day 0-84[b]	464.8	856.2	836.5	

a Data were obtained from Table 2 on pages 36-37 of the study report.
b Calculated by reviewers from data presented in this table
--- The 30 mg/kg/day group was killed for humane reasons on Day 36.

C. FOOD CONSUMPTION: There were no treatment-related effects on food consumption at any dose level. Sporadic increases ($p \leq 0.05$) were observed in the 7.5 and 15 mg/kg/day males; sporadic differences ($p \leq 0.05$) were observed in all treated groups in the females.

D. COMPOUND INTAKE: The actual dose of the test material to the dogs is presented in Table 1.

E. OPHTHALMOSCOPIC EXAMINATION: There were no treatment-related findings observed during the ophthalmoscopic examinations.

F. BLOOD ANALYSES

1. **Hematology:** No adverse, treatment-related findings were observed in the examined hematology parameters. On Day 28, hematocrit was increased ($p \leq 0.05$) in all treated females by 6-9%; and on Day 56, hemoglobin was increased ($p \leq 0.05$) in the 7.5 and 15 mg/kg/day females by 9%. However, these parameters were similar to controls in all groups on Day 89 and were considered to be transient. All other differences ($p \leq 0.05$) were unrelated to dose.

2. **Clinical chemistry:** No adverse, treatment-related findings were observed in the examined clinical chemistry parameters. On Day 28, lactate dehydrogenase was decreased ($p \leq 0.05$) by 44-48% in the 15 mg/kg/day and above females; however, decreases in this parameter are not usually considered adverse. All other differences ($p \leq 0.05$) were unrelated to dose.

G. URINALYSIS: There were no adverse, treatment-related urinalysis findings. On Day 55, urine volume was increased ($p \leq 0.05$) in the 7.5 and 15 mg/kg/day males by 101-185%; however, in the absence of corroborating findings of toxicity, this increase was considered equivocal. Protein was increased ($p \leq 0.05$) in all treated females on Day 27 (15-25 mg/dL treated vs. 0 controls); however, these findings were within the range of historical controls (0-100 mg/dL) and were considered incidental. All other differences ($p \leq 0.05$) were unrelated to dose.

H. SACRIFICE AND PATHOLOGY

1. **Organ weight:** There were no adverse, treatment-related effects on organ weights. Absolute liver weights were increased ($p \leq 0.05$) by 20-29% in the 7.5 and 15 mg/kg/day males; however, relative (to body) liver weights were similar to controls, and there were no corroborating gross or microscopic findings. Therefore, these increases were considered equivocal. All other differences were unrelated to dose.

2. **Gross pathology:** There were no effects of treatment observed at necropsy. Prostate reduced in size was observed in two 30 mg/kg/day males; this finding correlated with a microscopic finding of immature physiologic status, due to the age at which these dogs were killed. All other gross pathological findings were observed in a single animal and/or were not corroborated by microscopic pathological findings.

3. **Microscopic pathology:** Microscopic pathological findings are presented in Table 3. Treatment-related findings were observed in the nervous system at 15 and 30 mg/kg/day, and were characterized as a focal/multifocal axonal degeneration. In the males (compared to 0 controls): slight multifocal axonal degeneration of the sciatic nerve was observed in 1/4 dogs at 15 and 30 mg/kg/day; and minimal to moderate multifocal axonal degeneration of the spinal cord was noted in 1/4 dogs at 15 mg/kg/day (minimal severity) and 4/4 dogs at 30 mg/kg/day. In the females (compared to 0 controls): minimal to slight multifocal axonal

degeneration was observed in the brain in 1/4 dogs at 15 mg/kg/day (minimal severity) and 2/4 dogs at 30 mg/kg/day; minimal to slight focal/multifocal axonal degeneration was observed in the sciatic nerve in 2/4 dogs at 15 mg/kg/day (minimal severity) and 2/4 dogs at 30 mg/kg/day; and minimal to moderate multifocal axonal degeneration of the spinal cord was noted in 2/4 dogs at 15 mg/kg/day (minimal and moderate severity) and 4/4 dogs at 30 mg/kg/day. All other microscopic findings were observed in a single dog, were minimal in severity, and/or were commonly observed findings in dogs.

TABLE 3. Selected micropathological findings in the nervous system of dogs administered BCS-AA10717 by oral gavage for up to 90 days[a]

Study Day			Dose (mg/kg/day)			
			0	7.5	15	30
Males						
Sciatic nerve	axonal degeneration, multifocal	Slight	0/4	0/4	1/4	1/4
Spinal cord	axonal degeneration, multifocal	Total	0/4	0/4	1/4	4/4*
		Minimal	0/4	0/4	1/4	2/4
		Slight	0/4	0/4	0/4	1/4
		Moderate	0/4	0/4	0/4	1/4
Females						
Brain	axonal degeneration, multifocal	Total	0/4	0/4	1/4	2/4
		Minimal	0/4	0/4	1/4	1/4
		Slight	0/4	0/4	0/4	1/4
Sciatic nerve	axonal degeneration, focal/multifocal	Total	0/4	0/4	2/4	2/4
		Minimal	0/4	0/4	2/4	1/4
		Slight	0/4	0/4	0/4	1/4
Spinal cord	axonal degeneration, multifocal	Total	0/4	0/4	2/4	4/4*
		Minimal	0/4	0/4	1/4	1/4
		Slight	0/4	0/4	0/4	1/4
		Moderate	0/4	0/4	1/4	2/4

a Data were obtained from pages 23, 285, 288, 291, and 480-520 of the study report.
* Significantly different from controls; $p \leq 0.05$

III. DISCUSSION and CONCLUSIONS

A. INVESTIGATORS' CONCLUSIONS: In this study, compound-related effects were seizures in the 30 mg/kg/day males and females and morphologic changes characterized as axonal degeneration noted particularly within the sensory tract of the dorsal spinal cord, with much less involvement of the sciatic nerve and brain stem. These lesions were present in both sexes of the 30 mg/kg/day group, with some affected animals in the 15 mg/kg/day group. The LOAEL for this study is 15 mg/kg/day.

B. REVIEWERS' COMMENTS: No adverse, treatment-related effects were observed on food consumption, ophthalmoscopic examinations, hematology, clinical chemistry, urinalysis, organ weights, or gross pathology.

At 30 mg/kg/day, three dogs (male DL3004, female DL3102, and female DL3103) presented with seizures on Days 15, 22, and 35, respectively, and were killed on the day the seizures were observed. Treatment-related clinical findings observed in these dogs were as follows: male DL3004, seizures; female DL3102, aggressive, tremors, ataxia (unsteady), labored

breathing, left pupil no reaction to light, right pupil sluggish, seizures, and sores due to seizures; female DL3103, aggressive, tremors, ataxia (unsteady), decreased activity, circling, pupils sluggish, and seizures. Due to the seizures, dosing of the 30 mg/kg/day group was halted on Day 35, and the surviving dogs of this group were euthanized on Day 36 for humane reasons. Additionally at this dose, male dogs displayed decreased body weight gains for Days 0-35 compared to all other groups (57.7 g compared to 508.2-719.0 g), while females lost weight (-76.3 g) during this period compared to the other groups (51.3-489.3 g).

Treatment-related findings were observed in the nervous system at 15 and 30 mg/kg/day, and were characterized as a focal/multifocal axonal degeneration. In the males, slight multifocal axonal degeneration of the sciatic nerve was observed in 1/4 dogs at 15 and 30 mg/kg/day, and minimal to moderate multifocal axonal degeneration of the spinal cord was noted in 1/4 dogs at 15 mg/kg/day (minimal severity) and 4/4 dogs at 30 mg/kg/day, both compared to 0 controls. In the females, minimal to slight multifocal axonal degeneration was observed in the brain in 1/4 dogs at 15 mg/kg/day (minimal severity) and 2/4 dogs at 30 mg/kg/day, minimal to slight focal/multifocal axonal degeneration was observed in the sciatic nerve in 2/4 dogs at 15 mg/kg/day (minimal severity) and 2/4 dogs at 30 mg/kg/day, and minimal to moderate multifocal axonal degeneration of the spinal cord was noted in 2/4 dogs at 15 mg/kg/day (minimal and moderate severity) and 4/4 dogs at 30 mg/kg/day, all compared to 0 controls.

The LOAEL is 15 mg/kg/day, based on axonal degeneration in the nervous system of both sexes. The NOAEL is 7.5 mg/kg/day.

This study is classified **acceptable/guideline** and satisfies the guideline requirements (OPPTS 870.3150; OECD 409) for a subchronic oral toxicity study in dogs.

C. **STUDY DEFICIENCIES:** The following minor deficiencies were noted but do not affect the conclusions of this review:

- Minimal information was provided for the dose selection rationale. In particular, the other dose levels used in the range-finding study were not provided; therefore, the reviewers could not determine if the doses selected for use in the definitive study, particularly the high dose, were appropriate.

- The sampling procedure for the homogeneity analyses was not described. Samples are normally taken from the top, middle, and bottom of the preparation.